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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/772,768
Filing Date: February 04, 2004
Appellant(s): HORWITZ, DAVID A.

Gargi Talukder
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/12/09 and supplemental appeal brief filed 3/31/09, appealing from the Office action mailed 4/14/08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Hall et al. (of record).

Hall et al. teach CD4+ suppressor T cells capable of inhibiting restoration of transplant rejection (i.e. decreasing transplant rejection, see in particular page 154, summary, lines 7-8). Additionally, Hall et al. teach CD4+ suppressor T cells to be CD45R (see in particular page 152, 2nd paragraph, line 1) and that $CD45R^+$ cells to be naïve cells (i.e. naïve CD4+ T cells, see in particular page 152, 2nd paragraph, lines 14-15). Hall et al. also teach that the suppressor T cells are IL-2R+ (i.e. CD25+, see page 149-150). However, Hall et al. do not teach the same process of making the claimed suppressor T cells. As regards to Appellant's reliance upon product-by-process limitations of the claims; it is noted that the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113. The claimed product is the same product as taught by Hall et al., irrespective of how it is made.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Groux et al., 1997, in view of Seder et al., 1998.

Groux et al. teach a population of regulatory T cells (i.e. suppressor T cells) made by incubating a CD4+ enriched population of PBMC with irradiated allogenic monocytes (i.e. a donor population of mononuclear cells depleted of T cells, see page 739 in particular). Groux et al. also teach that the suppressive activity of the cells is mediated by their production of TGF-beta (see page 70 in particular).

Groux et al. do not teach incubating the CD4+ T cells with TGF-beta.

Seder et al. teach that incubating CD4+ T cells with TGF-beta enhances the production of TGF-beta by the T cells.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add TGF-beta, as taught by Seder et al. to the cultures of regulatory T cells taught by Groux et al. The ordinary artisan at the time the invention was made would have been motivated to do so in order to enhance TGF-beta production by the regulatory T cells, since Groux et al. teach that the suppressive activity of the regulatory T cells is mediated by their production of TGF-beta, and Seder et al. teach that culture with TGF-beta enhances TGF-beta production by T cells. Furthermore, claim 5 is included since PBMC enriched for CD4+ cells are enriched for naïve CD4+ T cells compared to the starting population of PBMC. Claim 3 is included since the patentability of a product does not depend on its method of production, and Groux et al. and Seder et al. make obvious the suppressor T cells of the instant claims.

(10) Response to Argument

Regarding the rejection under 35 U.S.C. 102, Appellant argues that the cells taught by Hall et al. require radioresistant CD8+ cells to mediate their suppressive effect, while the instant cells exhibit suppressive activity independent of CD8+ cells.

Hall et al. teach a CD4+CD25+ cell population that suppresses graft rejection after in vivo administration. Hall et al. further teach that when the graft recipient is depleted of radioresistant CD8+ cells, the administered CD4+ cells do not suppress graft rejection to a statistically significant degree. Appellant asserts that the suppressor cells of the instant claims are different from those of Hall et al., since they mediate their suppressive effect independent of CD8+ T cells. As an initial matter, it is noted that the instant claims are not limited to CD4+ suppressor T cells that mediate suppression independent of CD8 cells. In fact, claims 1 and 2 specify that the starting population of cells for producing the suppressor T cells are PBMCs. PBMCs comprise CD8 T cells (see, for example, page 9 of the instant specification), and thus the method for producing the claimed product involves culturing a cell population comprising CD8 T cells. However, even when the claims are limited to making the claimed suppressor

cells with a CD4+ enriched population of PBMC, Appellant has not provided any evidence that the cells of the instant claims can mediate suppression in vivo in a host depleted of radioresistant CD8 cells, which would distinguish the cells of the instant claims from those of Hall et al. Appellant cites Zheng et al., Fig. 8, as evidence of the CD8 independent of the claimed cells. However, the suppressor cells of Zheng et al. are not the cells of the instant claims, since they are suppressor cells made by culture of CD4+ T cells with SEB and TGF-beta. Appellant also cites Example 1 of the instant specification as evidence of the CD8 independence of the claimed suppressor cells. Example 1 merely describes a method of producing suppressor cells and does not provide evidence that the claimed suppressor cells function in the absence of CD8 cells, as asserted by Appellant. Moreover, the suppressor cells in Example 1 were produced by culturing CD4+ T cells with irradiated PBMCs. As noted above, PBMC comprise CD8 cells. Thus, the suppressor cells of Example 1 were produced in the presence of CD8+ cells. Appellant further cites Fig 2A and 4B as evidence that the claimed suppressor cells are able to function even in the absence of CD8+ cells. These assays involve testing the ability of suppressor T cells to inhibit in a culture that includes CTL (i.e. CD8+ cells). Again, CD8+ cells are present in these in vitro assays. Thus, the examples cited by Appellant do not demonstrate that the claimed suppressor cells can function in the absence of CD8 cells, as all of the in vitro experiments of the specification comprise CD8 cells. Appellant has not provided any evidence that the suppressor cells of the instant claims differ from those of Hall et al. While the suppressor cells in the examples of the specification are themselves CD4+ and not CD8+, this is not evidence that the cells mediate suppression "independent of CD8+ cells" as asserted by Appellant. Moreover, the suppressor cells of Hall et al. that suppress graft rejection are a CD4+ population of cells that meet all the structural requirements of the instant claims (i.e. suppress graft rejection of a solid organ and are CD4+CD25+ cells).

Appellant further argues that Hall et al. uses T cells from cyclosporine treated animals to produce suppressor T cells, and the use of cyclosporine inhibits Foxp3.

Appellant further notes that the cells of the instant claims are Foxp3+, which distinguishes the cells of the instant claims from those of Hall et al.

The instant claims are not limited to a FoxP3+ suppressor cell, and Appellant has not provided any evidence that the cells of the instant claims are FoxP3+. Appellant cites Zhang et al. as evidence that TGF-beta induced suppressor cells are FoxP3+. However, Zhang et al. teach that FoxP3 is expressed by naturally occurring CD4+CD25+ regulatory T cells. Zhang et al. does not provide any evidence that cells made by the method recited in the instant claims (i.e. culture of donor and recipient PBMC with TGF-beta) develop into FoxP3+ suppressor T cells. Appellant further cites the Horwitz declaration of 6/11/07 as evidence of the fact that the suppressor T cells of the instant claims express FoxP3. However, the Horwitz declaration demonstrates that a CD8+ suppressor T cell expresses FoxP3. The instant claims are not drawn to CD8+ suppressor T cells, but rather CD4+ suppressor T cells. There is no evidence of record that the process of the instant claims results in the production of a FoxP3+ suppressor T cell, and the instant claims are not limited to suppressor T cells that are FoxP3+.

Regarding the rejection under 35 U.S.C. 103, Appellant argues that Groux et al. do not teach that the regulatory T cells mediate their suppressive activity via TGF-beta, but that TGF-beta inhibits the proliferation of the regulatory T cells themselves. Thus, Appellant concludes that there would be no motivation to increase the amount of TGF-beta produced by the regulatory T cells by the method of Seder et al.

Groux et al. teach regulatory T cells (Tr1 cells) that produce IL-10 and TGF-beta (see page 738). Groux et al. further teach that the ability of the regulatory T cells to suppress antigen specific T cell responses is predominantly mediated by IL-10 and TGF-beta production (see page 740, column 2, first full paragraph). Thus, in contrast to Appellants assertions, Groux et al. clearly teach that the regulatory T cells function to suppress immune responses by their production of the cytokines IL-10 and TGF-beta. Seder et al. teach that incubating CD4+ T cells with TGF-beta enhances the production of TGF-beta by the T cells. Thus, the ordinary artisan would have been motivated to

include TGF-beta in the cultures for producing the regulatory T cells of Groux et al., in order to enhance TGF-beta production by the resulting regulatory T cells.

Appellant further argues that Groux et al. teach away from the claimed invention, since they demonstrate that anti-TGF-beta antibodies augment proliferation of regulatory T cells. Thus, Appellant concludes there would be no motivation to add TGF-beta in a method of generating regulatory T cells, since it would be expected to inhibit their in vitro expansion.

The ordinary artisan would be motivated to add TGF-beta to the cultures for the reasons set forth above. Additionally, in contrast to Appellants assertions, Groux et al. teach that anti-TGF-beta antibodies alone do not effect the proliferation of regulatory T cells generated by stimulation with allogeneic monocytes (see Fig. 2b, JDV23 TR1 cells). While Groux et al. teach that anti-TGF-beta antibodies can augment proliferation of regulatory T cells stimulated by other methods (for example with anti-CD3), this is not relevant, since the instant claims are not drawn to anti-CD3 stimulated suppressor T cells, but those made by stimulation with donor (i.e. allogeneic) mononuclear cells. Additionally, Groux et al. teach that even under circumstances where cytokines might inhibit regulatory T cell expansion (as is the case with IL-10, for example), it is still advantageous to include them in the cultures if they induce the cells to acquire regulatory T cells functions (see page 738, in particular). Furthermore, Groux et al. teach that after acquisition of regulatory function in the presence of suppressive cytokines such as IL-10, the regulatory T cells can be expanded in IL-2 (see page 741, in particular). Thus, even in situations where cytokines might inhibit the proliferation of the regulatory T cells themselves, Groux et al. teach that it is nevertheless advantageous to use said cytokines if they induce regulatory functions , and that any inhibitory effects of said cytokines can readily be overcome by subsequent addition of IL-2. Additionally, as noted above, based on the teachings of Seder et al., one of ordinary skill in the art would have been motivated to add TGF-beta to induce higher levels of TGF-beta production from the regulatory T cells, which would lead to enhanced suppressive capacity of the cells based on the teachings of Groux et al. (i.e. the references teach that addition of TGF-beta would be expected to induce regulatory

functions).

Appellant further argues that the cells made obvious by Groux et al. and Seder et al. are not the cells of the instant claims. Appellant notes that the cells of Groux et al. are Tr1 cells producing IL-10, while the instant suppressor cells are CD4+CD25+. Appellant notes that as evidenced by Roncarolo et al., Tr1 cells are not the same as CD4+CD25+ T cells

Appellant's arguments that the cells of Groux et al. are different from those of the instant claims are not relevant, since the rejection is based on a combination of Groux et al. and Seder et al. (i.e. one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references). Nevertheless, it is noted that Roncarolo et al. teach that activated Tr1 cells do express IL-2Ra (i.e. CD25, see page 30, left column). Thus, the activated Tr1 cells of Groux et al. are CD25+, as recited in the instant claims.

Appellant further notes that nothing in Seder et al. indicates that the method produces the presently claimed suppressor cells, and in fact Seder et al. also teach priming T cells with IL-10, which induces Tr1 cells.

It appears that Appellant is arguing that the presence of IL-10 precludes the generation of suppressor T cell of the instant claims. However, the instant suppressor cells are made by a process comprising culturing donor and recipient PBMC in a regulatory composition "comprising" TGF-beta. Thus, the claims encompass additional unrecited elements as part of the regulatory composition. Furthermore, the instant specification discloses on page 10 that the regulatory composition can comprise IL-10, and thus, the presence of IL-10 does not render the regulatory T cells of Groux et al. and Seder et al. to be different from those of the instant claims. In fact, Groux et al. and Seder et al. make obvious a regulatory T cell with all the structural features (i.e. CD4+CD25+) of the instant claims, and produced by a process identical to that recited in the instant claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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